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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,302	03/23/2001	Deborah Ann Law	MPI98-1481USM	6919

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MILLENNUIM PHARMACEUTICALS, INC.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,302	LAW ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-91 and 93-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *79-81 and 94-99* is/are allowed.

6)☒ Claim(s) *76-78,82-91 and 93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-23-04 has been entered.

Applicants' amendment filed 7-23-04 has been entered. Claims 69-75 and 92 have been canceled. Claims 76-80, 83-89 and 93 have been amended. Claims 94-99 have been added. Claims 76-91 and 93-99 are pending and under consideration.

Double Patenting

2. Applicant is advised that should claim 90 be found allowable, claim 91 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 76-78, 82-91 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a transgene integrated into the genome and the transgene comprises DNA encoding a mutant GP IIIa (beta3) protein having **two** conservative amino acid substitutions for two wild type tyrosine residues in its mutant cytoplasmic domain, wherein said transgenic mouse has platelet with reduced or absent phosphorylation of said mutant GP IIIa protein compared to platelets with wild type GP IIIa protein, does not reasonably provide enablement for a transgenic mouse comprising a transgene integrated into the genome and the transgene comprises DNA encoding a mutant GP IIIa (beta3) protein having **a** conservative amino acid substitutions for a wild type tyrosine residues in its mutant cytoplasmic domain, wherein said transgenic mouse has platelet with reduced or absent phosphorylation of said mutant GP IIIa protein compared to platelets with wild type GP IIIa protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 76-78, 82-91 and 93 are directed to a heterozygous or homozygous transgenic mouse comprising a transgene integrated into the genome and the transgene comprises DNA encoding a mutant GP IIIa (beta3) protein having **a** conservative amino acid substitutions for a wild type tyrosine residues in its mutant cytoplasmic domain, wherein said transgenic mouse has platelet with reduced or absent phosphorylation of said mutant GP IIIa protein compared to platelets with wild type GP IIIa protein, a method of making said transgenic mouse, and a method of using said transgenic mouse.

The specification teaches the method of making a transgenic mouse comprising DNA encoding mutant GP IIIa (beta3) protein having **two** conservative amino acid substitutions for two wild type tyrosine residues (Y747F and Y759F) in its mutant cytoplasmic domain, and discusses that "if tyrosine phosphorylation pf GP IIIa is indeed a critical step in outside-in GP Iib-IIIa signaling, then it could be hypothesized that compounds capable of inhibiting such a phosphorylation event would have anti-thrombotic properties...a mutant mouse has been generated in which the endogenous GP IIIa gene was replaced with one in which the two cytoplasmic tyrosine residues were mutated to phenylalanines...plateles from such animals express GP IIIa that can not undergo tyrosine phosphorylation (specification, p. 14, 15, examples). The cited reference Law et al., 1999, in the amendment filed 1-2-02 shows that homozygous diYF platelets failed to aggregate when stimulated with 0.05 units/ml thrombin and no tyrosine phosphorylation of the beta3 ICY occurred, and heterozygous platelets consistently showed an intermediate phenotype (e.g. p. 808, right column, p. 809, left column). However, the specification fails to provide adequate guidance and evidence for the resulting phenotype of a transgenic mouse comprising DNA encoding mutant GP IIIa (beta3) protein having **a** conservative amino acid substitutions for a wild type tyrosine residue in its mutant cytoplasmic domain.

Y747F and Y759F are different amino acid substitutions at different locations of the cytoplasmic domain of GP IIIa protein. One amino acid substitution is different from two amino acid substitutions. Since heterozygous platelets of the transgenic mouse having mutant GP IIIa protein show an intermediate phenotype, it appears that there is no dominant negative effect of mutant GP IIIa protein, having Y747F and Y759F, on the wild type GP IIIa protein. The

specification fails to provide guidance and evidence for how Y747F and Y759F contribute to tyrosine phosphorylation and platelet aggregation independently, and whether Y747F or Y759F alone can result in the recited phenotype of the transgenic mouse, i.e. a transgenic mouse has platelets with reduced or absent phosphorylation of said mutant GP IIIa protein compared to platelets with wild type GP IIIa protein. There is no evidence of record that a transgenic mouse, heterozygous or homozygous, comprising DNA encoding a mutant GP IIIa (beta3) protein having **a** conservative amino acid substitutions for a wild type tyrosine residues in its mutant cytoplasmic domain, would have a phenotype of having platelets with reduced or absent phosphorylation of said mutant GP IIIa protein compared to platelets with wild type GP IIIa protein.

The state of the art in the fields of transgenic animal, including knockout and knock-in animals, at the time of the invention was unpredictable, the transgene expression and resulting phenotype of such expression is not always accurately predictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Sigmund, June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes

examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombinantion in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column).

In view of the inherent unpredictability of the resulting phenotypes of transgenic animals and the lack of evidence for the phenotypes of the claimed transgenic mice, one skilled in the art at the time of the invention would not know how to use the claimed transgenic mice and the cells derived from said transgenic mice.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

Claims 76-78, 82-91 and 93 are rejected. Claims 79-81 and 94-99 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.